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Formulation technologies to overcome poor drug-like properties

Overcoming poor permeability – the role of prodrugs for oral drug delivery

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Today, prodrugs are an important option in any lead optimization program and are being considered as soon as critical hurdles in terms of solubility and permeability are identified. A successful prodrug effort starts with a careful evaluation of the issues and is guided by a detailed stepwise characterization of solubility, stability and permeability to arrive at an efficient optimization process.

Introduction

The initial goal of a lead optimization program is to increase the affinity of the compounds at the target with an eye on maintaining the ligand efficiency as high as possible. This initial phase often leads to candidates with less than optimal physical or pharmacokinetic properties and commonly, a great deal of effort is devoted to improve the metabolic stability and the pharmacokinetic characteristics, such as *in vivo* half life. Unfortunately, this results frequently in pre-clinical leads with either poor solubility or suboptimal permeability or both, in other words in compounds belonging to the Biopharmaceutics Classification System (BCS) classes II–IV [1]. The medicinal chemists is at this point are searching for the ideal compound, one with the desired potency, the proper physical and pharmacokinetic properties. For compounds with poor solubility and/or low permeability, solutions are being sought with experts in formulations and options for prodrugs are being explored. Fortunately, it is now common that these alternate approaches are being investigated early on and form an integral part of late lead optimization programs. This review focuses on detailing the principles applied to the identification and optimization of prodrugs to either improve solubility or permeability, or both, and to employ recent examples as a guide through the discussion [2].

Before embarking on a prodrug effort it is imperative to fully understand the problem and to have a clear target in terms of dose and route of administration. With these prerequisites in place, an assessment is possible if a prodrug approach will likely be successful and which kind of prodrug should be investigated first – one to increase solubility or one to improve permeability or one to improve both.

A typical evaluation cascade in such an effort is shown in Fig. 1. The first tier consists of *in vitro* evaluations and will allow for an immediate assessment if progress toward improving solubility and lipophilicity is being made. A renewed search for novel prodrugs is initiated should an insufficient improvement in the measured property be observed at any step in the cascade. This iterative process will continue until a prodrug with acceptable properties is obtained to advance it to pre-clinical safety assessments. The branching indicated between prodrugs targeted at improving solubility from the ones improving permeability is shown to illustrate the point that not all tests need to be conducted at every step with every compound. An efficient screening paradigm will be flexible and concentrate on the most critical aspects at the given moment.

In Fig. 1, the Caco2 experiment stands for any test to assess permeability, including the assessment of the involvement of

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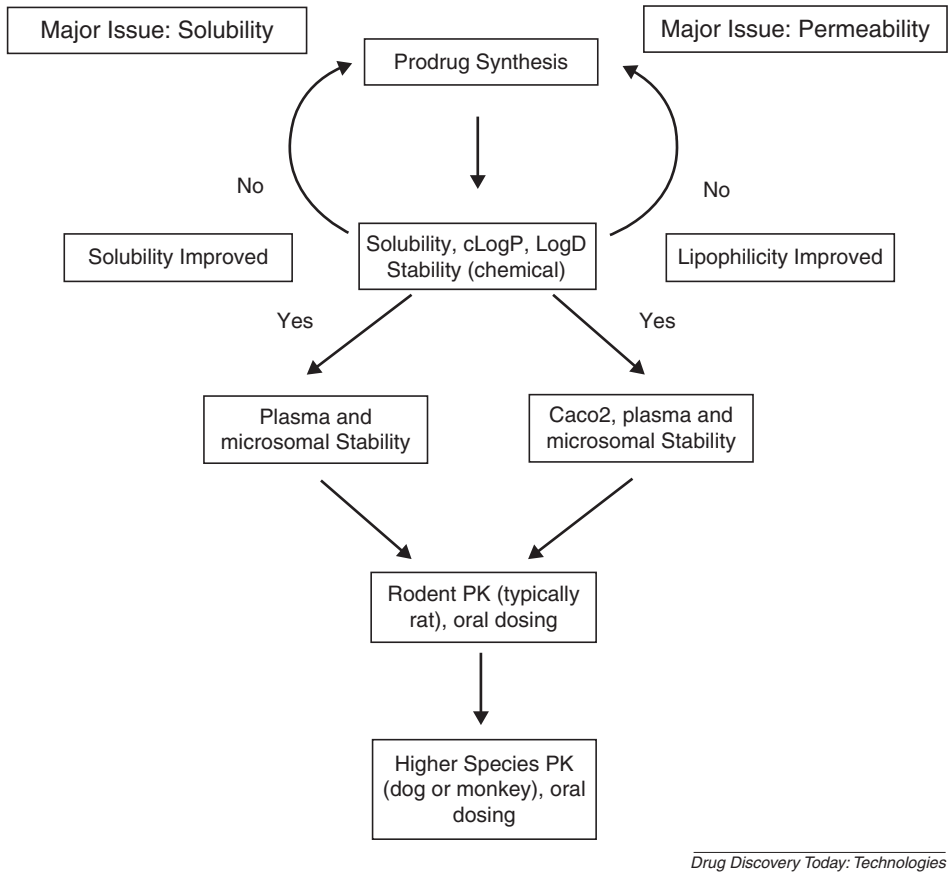

Figure 1. Typical evaluation cascade of prodrugs.

transporters; either influx, such as the human intestinal peptide transporter PEPT1, or efflux transporters, primarily PgP. Thus, such a test needs to be conducted with the appropriate controls to ensure the proper expression levels of transporter proteins. In Caco2 cells, this is routinely achieved at the level of 21 day cells, but not with cells after seven days of incubation.

All prodrugs, independent of route of administration, will need to fulfil as much as possible the following typical requirements:

(a) Prodrug attachment should add negligibly to the cost of goods; that is be based on easy synthesis and inexpensive prodrug moieties.
(b) The prodrug moiety should be readily cleaved in the desired tissue or cellular compartment. In most cases, the cleavage should be rapid and complete. Prolonged, slow cleavage may be desirable as a special form of a controlled release mechanism.
(c) The prodrug or the prodrug moiety should not add an additional side effect or toxicity burden to the parent drug; that is being readily excreted from the body and not possessing any inherent toxic potential.

Solubility and permeability

In addition to pre-systemic metabolism, a low oral bioavailability can be a result of either low solubility or low permeability or both. For an oral drug, a minimum solubility in the gastric environment is required. This is dependent on the dose necessary to achieve the desired therapeutic effect. Permeability has to be sufficient to deliver a therapeutically effective amount of drug into the portal vein. If the permeability is low, the greater the solubility of the drug has to be to result in the desired systemic exposure level. Thus solubility and permeability of oral drugs are necessarily linked and cannot be considered individually in isolation.

Prodrugs to enhance permeability of the parent drug

Many therapeutic agents are of a highly polar nature or are charged at physiological pH, which impacts the permeability significantly. Prominent examples among such compounds are carboxylic acids, strongly basic compounds such as amidines and guanidines, nucleosides and nucleotides, for the latter mainly analogs of nucleoside-monophosphates. For a comprehensive review, a number of recent reviews should be consulted [2]. Here, just a few recent examples are presented, with which the principles of such prodrugs are discussed.